

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule of an alternative splicing variant of a human voltage-gated calcium channel subunit, comprising a sequence of nucleotides encoding a voltage-gated calcium channel $\alpha 2\delta 2$ -a subunit selected from the group consisting of:
- (a) a sequence of nucleotides that encodes a human voltage-gated calcium channel $\alpha 2\delta 2$ -a subunit residues and comprises the sequence of nucleotides set forth in SEQ ID NO:1;
 - (b) a sequence of nucleotides that encodes a human voltage-gated calcium channel $\alpha 2\delta 2$ -a and that hybridizes under conditions of high stringency to the sequence of nucleotides set forth in SEQ ID NO:1;
 - (c) a nucleotide sequence varying from the nucleotide sequence specified in (a) or (b) as a result of degeneracy of the genetic code;
 - (d) a sequence of nucleotides having at least 95% sequence identity or is exactly complementary to the nucleotide sequence set forth in SEQ ID NO:1;
 - (e) fragments of (a), (b), c), or (d) that encodes polypeptide capable of forming a functional voltage-gated calcium channel.
2. An amino acid sequence selected from the group consisting of: (i) an amino acid sequence coded by the isolated nucleic acid sequence of alternative splice variants of claim 1; (ii) homologues of the amino acid sequences of (i) in which one or more amino acids has been added, deleted, replaced or chemically modified in the region, or adjacent to the region, where the amino acid sequences differs from the original amino acid sequence, coded by the original $\alpha 2\delta 2$ -a nucleic acid sequence from which the variant has been varied by alternative splicing.
3. A substantially pure polypeptide comprising an amino acid sequence as set forth in any one of SEQ ID NO:2 or 4.
4. A substantially pure polypeptide comprising an amino acid sequence encoded by the nucleotide sequence as set forth in one of as set forth in one of SEQ ID NO:1 or 3.

5. A substantially pure polypeptide which has at least 80 % identity to the amino acid sequence of SEQ ID NO:2, which may include up to N_a amino acid alterations over the entire length of SEQ ID NO:2, wherein N_a is the maximum number of amino acid alterations, and is calculated by the formula

$$N_a = X_a - (X_a Y),$$

in which X_a is the total number of amino acids in SEQ ID NO:2, and Y has a value of 0.80, wherein any non-integer product of X_a and Y is rounded down to the nearest integer prior to subtracting such product from X_a .

6. A purified antibody which binds to an amino acid sequence which is present only in the alternative splice variant comprising the amino acid sequence set forth in one of SEQ ID NO:2 or 4, but is not present in the amino sequence of reference $\alpha 2\delta$ -2 polypeptide.

7. An expression vector comprising the nucleic acid molecule of claim 1 operably linked to a regulatory nucleotide sequence that controls expression of the nucleic acid molecule in a suitable host cell.

8. A recombinant host cell transfected by the expression vector of claim 7.

9. A method for detecting the presence of a variant nucleic acid sequence of $\alpha 2\delta$ -a in a biological sample, comprising the steps of: (a) hybridizing to nucleic acid material in said biological sample the nucleic acid molecule of claim 1 under conditions favoring the formation of a hybridization complex; and (b) detecting said hybridization complex; wherein the presence of said hybridization complex correlates with the presence of an variant nucleic acid sequence in the said biological sample.

10. A method for identifying candidate compounds capable of binding to a $\alpha 2\delta$ -a subunit polypeptide and modulating its activity the method comprising: (i) contacting a candidate compound with the substantially pure polypeptide of SEQ ID NO:2, and (ii) determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.

11. A method for detecting a $\alpha 2\delta$ -2 variant in a first biological sample, comprising the steps of: (a) contacting a detectable probe with said biological sample suspected of containing said variant under conditions favoring the formation of a complex between said probe and any said variant; and (b) detecting said complex wherein the presence of said complex correlates with the presence of the desired amino acid in said biological sample.

12. A method for detecting the level of one or more $\alpha 2\delta$ -2 isoforms or a fragment thereof in a biological sample, comprising the steps of: (a) contacting with said biological sample with a detectable antibody having binding specificity for at least one of SEQ ID NO:2 or 4, thereby forming an antibody-polypeptide complex; and (b) detecting the amount of said antibody-polypeptide complex and normalizing said amount to provide the level of said amino acid sequence in the sample.

13. A method for inhibiting human voltage-gated calcium channel $\alpha 2\delta$ -a subunit activity in a mammalian cell comprising contacting the mammalian cell with an amount of a human voltage-gated calcium channel $\alpha 2\delta$ -a subunit inhibitor effective to inhibit calcium influx in the mammalian cell.

14. The method of claim 13, wherein the inhibitor is selected from the group consisting of an antibody which selectively binds the human voltage-gated calcium channel $\alpha 2\delta$ -a subunit polypeptide, an antisense nucleic acid which binds a nucleic acid encoding human voltage-gated calcium channel $\alpha 2\delta$ -a subunit polypeptide and a dominant negative human voltage-gated calcium channel $\alpha 2\delta$ -a subunit polypeptide.

15. A method for identifying lead compounds for a pharmacological agent useful in the treatment of disease associated with increased or decreased voltage regulated calcium influx mediated by a human voltage-gated calcium channel comprising:

- (i) providing a cell expressing a human voltage-gated calcium channel $\alpha 2\delta$ -a subunit polypeptide according to claim 3;
- (ii) contacting the cell with a candidate pharmacological agent under conditions which, in the absence of the candidate pharmacological agent, to thereby cause a first amount of voltage regulated calcium influx into the cell; and
- (iii) determining a test amount of voltage regulated calcium influx as a measure of the effect of the lead compounds for a pharmacological agent

on the voltage regulated calcium influx mediated by a human voltage-gated calcium channel, wherein (a) a the test amount of voltage regulated calcium influx which is less than the first amount indicates that the candidate pharmacological agent is a lead compound for a
5 pharmacological agent which reduces voltage regulated calcium influx and (b) wherein a test amount of voltage regulated calcium influx which is greater than the first amount indicates that the candidate pharmacological agent is a lead compound for a pharmacological agent which increases voltage regulated calcium influx.

10 16. The method of claim 15, further comprising loading said cell with a calcium-sensitive compound which is detectable in the presence of calcium, wherein the calcium-sensitive compound is detected as a measure of the voltage regulated calcium influx.

15 17. A method for identifying compounds which selectively bind a human voltage-gated calcium channel $\alpha 2\delta$ -2 subunit isoform comprising, (i) providing a test cell preparation, wherein said cell expresses a human voltage-gated calcium channel $\alpha 2\delta$ -2 subunit isoform, (ii) providing a control cell preparation, wherein said cell expresses a human voltage-gated calcium channel non- $\alpha 2\delta$ -2 subunit isoform, with the proviso that the cell in the cell
20 preparation is identical to the test cell except for the expression of a non- $\alpha 2\delta$ -2 isoform being expressed, (iii) contacting the test cell preparation and the control cell preparation with a compound, and (iv) determining the binding of the compound to the test cell preparation and the control cell preparation, wherein a compound which binds the test cell preparation but does not bind the control cell preparation is a compound which selectively binds the human voltage-gated
25 calcium channel $\alpha 2\delta$ -2 subunit isoform.

18. A diagnostic method for treating or correcting a disease state caused by a dysfunctional human voltage-gated calcium channel mediated by the polypeptide of claim 3, predicting an oncogenic potential of a sample of lung and colon cells, comprising:

- 30 (a) providing a sample of human lung or colon tissue; and
(b) determining, in the sample, levels of expression of a gene product expressed from a nucleotide sequence as set forth in SEQ ID NO:1 or 3 or a nucleotide sequence which hybridizes to the nucleotide sequence corresponding to SEQ ID NO:1 or 3 or its complement, wherein an

aberrant levels of said gene product relative to normal indicates the need for treatment.

- 5 cells, comprising:
19. A diagnostic method for predicting an oncogenic potential of a sample of
- 10 (a) determining, in the sample, levels of expression of a gene product expressed from a nucleotide sequence of SEQ ID NO. 1 or 3 or a sequence which hybridizes to one of the above sequences or its complement, wherein excessive or insufficient levels of expression of said gene product relative to normal is predictive of the oncogenic potential of said cells.
- 15 20. An isolated nucleic acid molecule of an alternative splicing variant of a human voltage-gated calcium channel subunit, comprising a sequence of nucleotides encoding a voltage-gated calcium channel $\alpha 2\delta 2$ -b subunit selected from the group consisting of:
- 20 (a) a sequence of nucleotides that encodes a human voltage-gated calcium channel $\alpha 2\delta 2$ -b subunit residues and comprises the sequence of nucleotides set forth in SEQ ID NO:3;
- (b) a sequence of nucleotides that encodes a human voltage-gated calcium channel $\alpha 2\delta 2$ -b and that hybridizes under conditions of high stringency to the sequence of nucleotides set forth in SEQ ID NO:3;
- (c) a nucleotide sequence varying from the nucleotide sequence specified in (a) or (b) as a result of degeneracy of the genetic code;
- 25 (d) a sequence of nucleotides having at least 95% sequence identity or is exactly complementary to the nucleotide sequence set forth in SEQ ID NO:3;
- (e) fragments of (a), (b), c), or (d) that encodes polypeptide capable of forming a functional voltage-gated calcium channel.